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An update on Brucellosis: Endemic and Potential Global Re-emerging Zoonotic and Foodborne Disease

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Abstract

Brucellosis is a re-emerging zoonotic disease, which spreads in different ways: respiratory (inhalation), contact, alimentary (consumption of unpasteurized milk and contaminated dairy products) or a combination of these. The disease has existed in the Republic of Macedonia since 1980, with over 12.000 reported and confirmed human cases. All neighbouring and many other European countries have also reported existence of brucellosis with significantly different incidence. Brucellosis remains a rare disease in EU/EEA. In 2014, 354 confirmed cases of brucellosis were reported by 18 EU/EEA countries. The highest rates were reported by Greece (135), Spain (60) and Portugal (50). The control of brucellosis is very complicated due to large reservoirs in domestic and wild animals. The control of animal brucellosis is imperative for the control of human brucellosis.

Keywords: *Brucella*, brucellosis, food-borne, re-emerging, reservoirs, zoonotic.

Резюме

Бруцелозата е възобновяващо се зоонозно заболяване, което се разпространява по различни начини: респираторно (инхалации), чрез контакт, чрез храна (консумация на непастьоризирано мляко и замърсени млечни продукти) или комбинация от тях. Съществуването на болестта в Република Македония е потвърдено от 1980 г. с над 12 000 съобщени и потвърдени случая с хора. Всички съседни и много други европейски държави също съобщават за наличие на бруцелоза със значителни различия в честота на проявление. Бруцелозата остава рядко заболяване в страните от Европейския съюз и страните от Източноевропейския регион. През 2014 г. са съобщени 354 потвърдени случая на бруцелоза от 18 страни от от тях. Най-много са случаите, регистрирани в Гърция (135), Испания (60) и Португалия (50). Контролът на бруцелозата е много труден поради големия брой на домашниите и диви животни, като резервоар на инфекцията. Контролът на бруцелозата при животните е задължителен с оглед контрола на заболяването при хората.

Introduction

In 450 BC Hippocrates gave the first description of the disease. Capasso presented proofs of bone lesions in humans killed during the eruption of Vesuvius in 79 AD, and of presence of bacteria with similar morphology as *Brucella* in carbonized cheese (Capasso, 2002). Marston was the first to describe brucellosis as a separate disease in 1859. David Bruce first isolated the agent (*Brucella melitensis*) in 1887 in Malta. Zammit indicated brucellosis as a zoonotic disease 18 years later.

About 60% of emerging human pathogens are defined as zoonotic. Brucellosis is one of the worldwide most common re-emerging zoonotic diseases (Godfroid *et al.*, 2005; Selleem *et al*., 2010) with over 500.000 new human cases per year, also a disease which is significantly changing the global ecological map with new strains, hosts and reservoirs (Pappas, 2010).

The disease was successfully eradicated in most of the developed countries but has remained endemic in others. Areas with high risk are the Mediterranean countries (Portugal, Spain, Italy, Greece, Turkey and North Africa), East Europe, Africa, the Middle East, South and Central America and the Caribbean (Taleski *et al*., 2002; Corbel, 2006). Several traditional endemic areas like France, Israel and most of the Latin American countries have accomplished control of brucellosis while in oth-

er parts of the world the situation has dramatically worsened (Syria, Mongolia, Iraqi, Saudi Arabia), (Papas *et al*., 2006). Over long periods, no reports on the epidemiological and epizootic situations from some countries were available.

Brucella species are classified as a category B pathogen, a potent bioweapon and the most common laboratory-acquired pathogen. Brucellosis primarily affects domestic and wild animals and is then transmitted to humans. The route of transmission may be respiratory, contact, alimentary (food or water) or a combination of these. Spreading through food is very important as it happens by consuming unpasteurized milk, and dairy products made of such milk.

Numerous diagnostic tests, from isolation, serologic tests to molecular diagnostics, have been developed. The *Brucella* genome has been completely sequenced, but recent detection of new species has instigated a number of queries about their origin, evolution and taxonomy, which indicates a need of revision of the global map of brucellosis. The optimal treatment of human brucellosis is continuously under debate (Ariza *et al*., 2007).

The aim of this study was designed to give some up-dated information on new *Brucella* strains and reservoirs, the current epidemiology situation, paths of transmission of the disease with respect to zoonotic and foodborne diseases, and the current successful measures for control and prevention of brucellosis in the Republic of Macedonia, a small country with a long history and experience as an endemic area.

Materials and Methods

Reviews, presentations of official data, reports, scientific papers and conference reports were analyzed and presented.

Results and Discussion

Until recently, the genus *Brucella* was considered to represent a genetically homogeneous and clonal group of bacteria associated with: 1.Terresterial mammalian hosts (classical strains *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*, *B. ovis*, *B. neotomae*), 2. Marine mammals (*B. ceti* and *B. pinnipedialis*), and 3. „Atypical", more recently identified (*B. microti*, *B. inopinata*, *B. papionis* and *B. vulpis*). All species are genetically highly related , > 99% (Holger *et al*., 2008; Holger *et al*., 2010; Audic *et al.*, 2011; Nymo *et al.,* 2011). The most infective terrestrial *Brucella* species are *B. meiltensis* and *B. abortus*, while *B. suis* is less pathogenic. New *Brucella* strains as marine mammals and atypical *Brucella* species represent a new zoonotic threat for humans.

Recently reported *brucellae* from amphibians (worldwide-distributed exotic frogs) are geneticall-ly highly diverse and might represent several new *Brucella* species or a link between free-living soil saprophytes and the pathogenic *Brucella.* Amphibian *brucellae* are capable of causing disease in different frog species ranging from localized manifestations to generalized infections. Frogs represent a new and ecologically significant natural host and reservoir (Eisenberg *et al*., 2011; Scholz *et al.*, 2016; Dahouk *et al.*, 2017).

Because of the potentiality of emergence of new species as human pathogens, brucellosis is a continuously re-emerging zoonotic disease. Brucellosis remains a rare disease in EU/EEA. In 2014, 354 confirmed cases of brucellosis were reported by 18 EU/EEA countries. The highest rates were reported by Greece (135), Spain (60) and Portugal (50), following by Germany (47), France (16), Sweden (16), (ECDC, 2016).

Fig. 1. Reported confirmed brucellosis cases: rate per 100 000 population, EU/EEA, 2014 (Source: Annual epidemiological report, ECDC, 2016)

Brucellosis has existed in R. Macedonia since 1980 with over 12.000 reported and confirmed human cases (Taleski *et al*., 2013). The disease exists in all neighbouring and some other European countries with significantly different incidence (Cekanjac *et al*., 2009; Obradovic and Velic, 2009; Nicoletti, 2010; Nenova *et al*., 2013).

B. melitensis biotype 2 was confirmed as an etiological agent in R. Macedonia. A recent study based on molecular methods for species typing (AMOS PCR and RT PCR), and genotyping (MLVA-16 and MLVA-8), beside *B. melitenisis,* also confirmed *B. abortus* (for the first time in

R. Macedonia). Epidemiological data suggested that about 23% of the disease had spread by the alimentary way (foodborne disease due to consumption of unpasteurized milk, cheese, and undercooked infected meat), 34% by contact and 43 % by a combined way of spreading brucellosis. The respiratory way is rare and happens in laboratories or while working with infected animals. About 80% of the patients lived in rural, and 20% in urban areas. The disease has a seasonal character in the Mediterranean area, with a maximum in May-June and minimum in winter. Since 2008, in R. Macedonia, the national control strategy has been completely changed from „test and slaughter" to vaccination of small ruminants (sheep and goats) with Rev 1 vaccine, applied intraocularly (Naletoski *et al*., 2009; Banai, 2010; Blasco, 2010). The results indicate a significant decrease in the epizooty in animals and human morbidity (287, 167, 107, 94, 47, 35, 20 and 23 human cases in 2009, 2010, 2011, 2012, 2013, 2014, 2015 and 2016, respectively).

a soil-associated motile bacterium to a host-adapted pathogen. Whilst there is no evidence to date that frog's isolates represent a zoonotic threat, appropriate measures should be taken to avoid unnecessary contact with potentially infected amphibians until the zoonotic potential of this group is better understood.

Control of animal brucellosis is imperative for control of human brucellosis. Preventive measures include effective veterinary and health control of animals (trading, transport, slaughter, vaccination) and animal products (meat, milk and their products), education of the population, multi-institutional cooperation and continuous state financial support. Exchanges of positive and successful experience and collaboration of all countries in endemic areas is imperative, beside international help with resources and expertise.

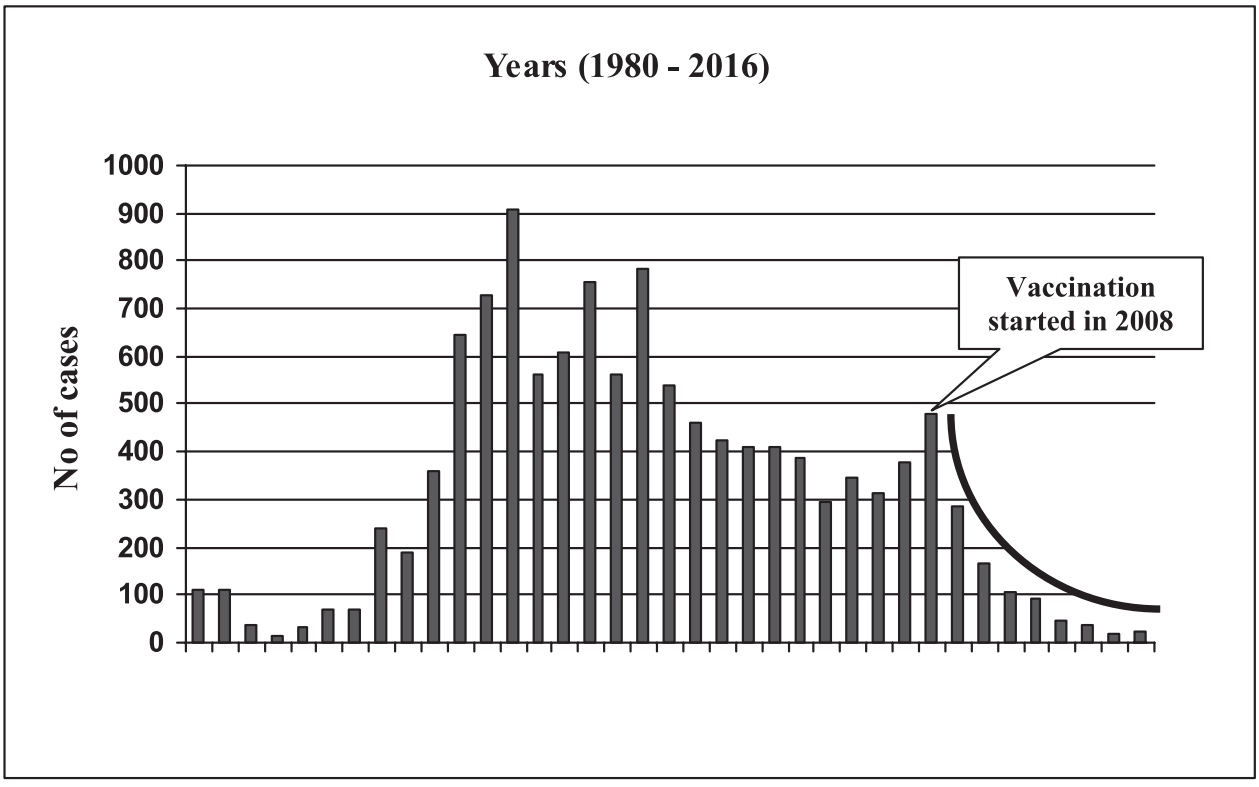

Fig. 2. Human cases in Macedonia

Conclusions

Control of brucellosis is very complicated due to large and novel reservoirs in domestic and wild animals.

New *Brucella* species (marine mammals) as well as "atypical" *Brucella* strains have enhanced the understanding of the evolution of the genus from

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